REMARKS

A check for the fee for a two month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050.

Claims 67-69, 73-85, 87, 90-110, 112 and 113 are pending in the instant application. Claims 67, 85 and 99-102 are amended. Claim 67 is amended to recite that the method is for treating chronic sinusitis in order to render it clear that the method is for treating chronic sinusitis. Basis for the amendment to claim 67 can be found throughout the specification, for example, at page 1, paragraph 2. Claim 85 is amended to provide proper antecedent basis. Claims 85 and 99-102 are amended to render them clear. Claims 88, 89 and 111 are cancelled without prejudice or disclaimer

The Examiner's attention is directed to the Information Disclosure Statements of record. Included among citations is a listing of copending applications and an issued patent that are co-owned and/or have an inventor in common an. These include U.S. Patent No. 6,576,224, U.S., U.S. application Serial No. 10/193,081, which published as US 2002-0197212 and U.S. application Serial No. 10/231,804, which published as US 2003-0031631, and the published PCT application WO/0102024.

REJECTION OF CLAIMS 67-69 and 73-113 UNDER 35 U.S.C. §103(a)

Claims 67-69 and 73-113 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rubin *et al.* (U.S. Patent No. 5,925,334) in view of Schmitt *et al.* (U.S. Patent No. 4,950,477) and Saunders Manual of Medical Practice (referred to hereinafter as Saunders Manual) Rubin *et al.* teaches a surfactant mixed with an aerosolizing agent to promote mucus clearance and further, that the use of surfactants lowers surface tension to enhance distribution and spreading of other medications to the lower respiratory tract. The Office Action

alleges that Schmitt *et al.* teaches administration of non-antimicrobial antibiotic such as amphotericin B by aerosol spray to prevent pulmonary infection. It is also alleged that Schmitt *et al.* teaches particle size of polyene between 0.5 μm and 8.0 μm are important for the polyene to reach and be retained in the lungs. The Office Action alleges that the Saunders Manual teaches the state of the art regarding treatment of sinusitis including antibiotics, decongestants, mucolytics, other ciliator activators, nasal corticosteroids, antihistamines and saline.

The Office Action then alleges that it would have been obvious to a person of ordinary skill in the art to have combined the surfactants/antibiotics/anti-inflammatory agents of Rubin *et al.* with the non-antibiotic antimicrobial agent and particle size of Schmitt *et al.* and the other agents disclosed in the Saunders Manual such as antibiotics, decongestants, mucolytics, nasal corticosteroids, and antihistamines to treat sinusitis with reasonable expectation of preparing formulations with multiple active agents which make the treatment more effective and potent. Further, the Office Action alleges that one of ordinary skill in the art would have been motivated to optimize the osmotic pressure, pH and NaCl equivalency of the composition by routine experimentation to include a wider range of different drugs.

The present Office Action further alleges that the compositions used in the claimed methods are taught by Rubin *et al.* because it is alleged that Rubin *et al.* teaches an anti-inflammatory agent that is inhaled for obstruction of the upper respiratory tract. The Office Action then alleges that if Applicant's surfactant acts in a different way, it is not claimed. The Office Action further states that if the prior art discloses the identical composition, the properties that the applicant discloses and/or claims are necessarily present.

This rejection is respectfully traversed.

Relevant Law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the

combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

The claims of the instant application are directed to methods of treating chronic sinusitis. Independent claim 67 is directed to a method of treatment of chronic sinusitis by nasally administering a pharmaceutical composition containing surfactant to a mammal diagnosed or suspected of having chronic sinusitis by administering an aerosolized composition and effecting deposition, penetration or retention of the composition in the nasal sinuses to thereby treat chronic sinusitis. The composition, which is formulated for nasal administration as an aerosol, contains betamethasone and a surfactant, and has a surface tension effective for deposition, penetration or retention of the composition in the nasal sinuses and is effective for treating chronic sinusitis.

Claims 68, 69 and 73-113 are dependent on claim 67 and thus include all elements of claim 67. The dependent claims further specify species and properties of surfactants and composition properties including surface tension, osmolality, pH, NaCl equivalency, and particle size. Dependent claims also specify the addition of a second agent, combinations thereof and particular species thereof and methods of administration.

Differences Between the Claims and the Teachings of the Cited References

All of the claims include as requisite elements nasally administering an aerosolized pharmaceutical composition that has a surface tension effective for deposition, penetration or retention of the composition in the nasal sinuses to a mammal diagnosed or suspected of having chronic sinusitis. As discussed below, each of the references is deficient in failing to teach elements of the instant claims, including methods for treatment of chronic sinusitis nor any requisites therefor. Consequently, as established below, the combination of teachings of the cited references does not result in the instantly claimed methods.

Rubin *et al.* (US 5,925,334)

Rubin *et al.* is directed to methods for treatment of the lungs, particularly treatment of the lower respiratory tract. Rubin *et al.* is directed to compositions of pulmonary surfactants and their use in treatment of lung diseases, such as cystic fibrosis. Rubin *et al.* teaches that pulmonary surfactant is essential for mucus clearance in the lung and that in many pulmonary diseases associated with hypersecretion there is an inactivation of surfactant by inflammatory mediators. Rubin *et al.* teaches administration of pulmonary surfactant to patients with cystic fibrosis or chronic bronchitis to enhance mucus clearance and improve pulmonary function.

Rubin *et al.* teaches methods that promote lung airway clearance for applications including mucus clearance, meconium aspiration syndrome and sleep apnea by providing pulmonary surfactant. Thus, Rubin *et al.* is directed

to methods and surfactant compositions for treating the **lower respiratory tract** (column 10, lines 14-19). Rubin *et al.* discusses the use of the surfactant compositions with anti-inflammatory agents for treatment of patients with conditions of upper respiratory obstruction, the use of the surfactant is "to enhance the distribution of inhaled anti-inflammatory agents...to the lower respiratory tract" (column 10, lines 26-34).

Rubin *et al.* is concerned with delivery of such agents to the lower respiratory tract. Rubin *et al.* teaches:

> Close to the time of birth, the developing lung is producing more and more pulmonary surfactant in the distal airways (alveoli) and this surfactant prevents these tiny airways from collapsing with each breath. Babies born prematurely often have insufficient production of pulmonary surfactant to keep the lungs open with each breath and this condition is called respiratory distress syndrome of the newborn. Because this disease claims the lives of thousands of prematurely born babies in the United States every year, many investigators have actively identified the components of pulmonary surfactant and developed a variety of surfactant products for administration to the prematurely born infant. This strategy has proven to be highly successful and has drastically reduced mortality in these tiniest of babies. Commercial products developed as pulmonary surfactant for newborns all include the phospholipid chemical, dipalmitoyl phosphatidylcholine (DPPC) as well as spreading agents that either occur naturally (surfactant associated proteins) or that are made artificially. Commercially available pulmonary surfactants are either made by extraction of natural surfactant from newborn animal lungs, generally cows or pigs (Survanta, Curosurf, Infasurf, BLIS), or made entirely in the laboratory from DPPC with other drugs added to enhance spreading, (Exosurf, KL4). All of these agents have been demonstrated to be effective and sale in the treatment of respiratory distress syndrome of the newborn. Pulmonary surfactants have also been administered to a large number of adults with severe respiratory failure due to a condition known as adult respiratory distress syndrome (ARDS). Despite laboratory confirmation that pulmonary surfactant is inactivated in this condition, these clinical trials have generally proven to be disappointing.

> The (B. K.) research laboratory* has long focused on understanding the mechanisms of mucus secretion and clearance. In persons with a chronic inflammatory lung diseases including cystic fibrosis, chronic bronchitis, diffuse panbronchiolitis, asthma, and bronchiectasis there is a massive increase in the number and size of mucus secreting glands and cells with markedly increased production of mucus. This problem is made worse by damage to the airways leading to poor clearance of secretions. The build up of these mucus secretions in the airway further increases the amount of infection and inflammation, leads to increased difficulties in breathing, and can be associated with destruction of lung tissue. It is acknowledged that retention of airway secretions is an extremely important factor in the development of chronic lung disease and that medications to enhance clearance of these secretions could be of significant therapeutic benefit with potential to help tens of millions of Americans every year.
>
> Research has shown that surfactant is not only produced in the alveoli but that surfactant phospholipids are also secreted from the mucus glands and larger airways. We have demonstrated that airway surfactant is essential for mucus clearance and we further demonstrated that in many of the pulmonary diseases associated with hypersecretion there was inactivation of surfactant by inflammatory mediators. Because of this we hypothesized that the administration of pulmonary surfactant to patients with cystic fibrosis or chronic bronchitis would enhance mucus clearance and improve pulmonary function.

Thus, Rubin *et al.* is directed to methods for treatment of lung disorders that involve problems in the lungs resulting from inactivation of lung surfactant. There is no teaching that this is an issue with respect to the nasal passages nor that problems in treating chronic sinusitis derive from such problems.

There is no suggestion in Rubin *et al.* for treatment of the nasal passages nor for treatment of chronic sinusitis. The Examiner alleges that Rubin *et al.* teaches the use of surfactants to lower the surface tension of secretions in the airway, to enhance distribution and spreading of other medications to the lower respiratory tract for conditions such as sinusitis. It is respectfully submitted that that this statement is incorrect. Rubin *et al.* does not teach, suggest or mention the nasal passages nor sinusitis. Rubin *et al.* is directed to treatment of lung

disorders and use of pulmonary surfactant for such treatment. Furthermore, as described in the application and discussed below sinusitis and chronic sinusitis are different disorders.

Rubin *et al.* does **not teach or suggest any methods** for treatment of sinusitis or chronic sinusitis nor methods involving nasal administration, nor administration of compositions formulated for penetration or adherence to the nasal sinuses or cavity. Rubin *et al.* is solely directed to the use of pulmonary surfactants for treatment of lung diseases where there is an inactivation of lung surfactant as part of the etiology of the disease. Rubin *et al.* does not suggest treatment with aerosolized/atomized compositions of an agent for treatment of sinusitis with a surface tension that results in penetration or adhesion of the agent in the sinuses. Rubin *et al.* offers no teaching or suggestion for delivery of medications delivered to the sinuses, nor any teaching or suggestion of methods for treating **chronic** sinusitis.

Thus, the treatment of Rubin *et al.* is not for the treatment of chronic sinusitis or the nasal passages, but for treatment of the lungs to clear the airway obstruction in the upper respiratory tract and treat the lower respiratory tract. Rubin *et al.* is directed to methods for treatment of lung disorders that involve **problems in the lungs resulting from inactivation of lung surfactant**. There is no suggestion that inactivation of lung surfactant plays any role in chronic sinusitis. There is no suggestion or teaching in Rubin *et al.* that the difficulties encountered in treating chronic sinusitis or preventing its development has any relationship the problems associated with the **lack** of surfactant in the lung. Hence Rubin *et al.* fails to teach methods for treatment of sinusitis by adminstrating to the nasal passages an aerosolized composition that has a surface tension that results in penetration or adhesion of the agent in the composition in the sinuses, and effecting deposition, penetration or retention of the composition in the nasal sinuses to thereby treat chronic sinusitis. The secondary references fail to cure these deficiencies.

Schmitt *et al.* (U.S. Patent No. 4,950,477)

Schmitt *et al.* is directed to the use of polyene for prevention of a pulmonary fungal infection. Schmitt *et al.* teaches the administration to the lung of an aerosol spray of polyene or a pharmaceutically acceptable derivative such as amphotericin B (column 1, lines 60-66; column 4, lines 55-58). Schmitt *et al.* teaches the administration of particles of polyene such that the particles reach and are retained in the lungs (column 2, lines 50-63).

Schmitt *et al.* does nor teach or suggest methods of treating **chronic** sinusitis with compositions of betamethasone and a surfactant where the composition is formulated with a surface tension effective for deposition, penetration or retention in the nasal sinuses. Schmitt *et al.* also does not teach or suggest methods for treatment other than pulmonary infection, nor medications other than polyene.

The methods taught by Schmitt *et al.* are directed to delivering medications to the lungs; there is no suggestion for treatment of chronic sinusitis nor any methods for treatment of the nasal cavity nor methods that include effecting deposition, penetration or retention of a composition in the nasal sinuses to thereby treat chronic sinusitis.

Thus Schmitt *et al.* fails to cure the deficiencies in the teachings of Rubin *et al.* because Schmitt fails to teach or suggest any methods for treatment of chronic sinusitis nor the steps of nasally administering a composition with a surface tension effective for deposition in the sinuses and effecting deposition thereof nor effecting deposition, penetration or retention of a composition in the nasal sinuses to thereby treat chronic sinusitis.

Saunders Manual

The Saunders Manual does not cure the deficiencies in the teachings of Rubin *et al.* or Schmitt *et al.*, singly or in any combination thereof. Saunders Manual teaches general methods for diagnosing and treating sinusitis. It does not mention or address treatment of chronic sinusitis. It teaches various agents

for treatment of sinusitis, including oral antibiotics, systemic decongestants, nasal corticosteroids, which it states have a limited role, antihistamines and nasal saline and steam.

As described in the instant specification and known to those of ordinary skill in the art, sinusitis can be intractable to treatment. It often becomes a chronic disorder with acute flare-ups and can last for years; it is the chronic disorder to which the instantly claimed methods are directed. Saunders Manual does not address this problem.

Saunders Manual is directed to the diagnosis and treatment of acute sinusitis. Saunders Manual does not teach or suggest treatments for chronic sinusitis. As described in the instant application, chronic sinusitis differs from acute sinusitis. For example, chronic sinusitis lasts longer than three weeks and often continues for months (page 2, paragraph 5). Additionally, in some cases of chronic sinusitis, there is usually tissue damage whereas recurrent acute sinusitis leaves no significant damage. Chronic sinusitis is often more difficult to treat and therefore, treatments for acute sinusitis are often not effective for chronic sinusitis (page 5, paragraphs 14 and 15). Further, Saunders Manual also does not teach or suggest the use of any other composition characteristics such as particle size, osmolality, pH, NaCl equivalency, hydrophile-lipophile balance or surface tension for use in treating chronic sinusitis.

The Saunders Manual does not teach or suggest any methods or compositions for treatment of **chronic sinusitis** nor a prophylactic to prevent development of chronic sinusitis. The Saunders Manual does not teach treatments for sinusitis that prevent chronic sinusitis and/or treat chronic sinusitis. As described in the specification, sinusitis becomes a chronic recurrent disorder with acute episodes. As described in the application, the compositions and methods of this application are effective in treating chronic sinusitis and also as a prophylactic to prevent development of chronic sinusitis. The instantly claimed methods are for treatment of chronic sinusitis, which

develop when methods, such as those in the Saunder Manual fail to treat sinusitis.

The Saunders Manual does not teach or suggest that there are few if any effective treatments for chronic sinusitis. There is no suggestion that such problems are at all related to problems that one encounters in the deep airways due to low levels of lung surfactant. Hence, Saunders Manual provides no motivation, teaching or suggestion to modify its compositions or methods, since it provides no suggestion that such are ineffective for chronic sinusitis.

Further, the Saunders Manual does not teach any aerosolized/atomized compositions of an agent for treatment of sinusitis nor any compositions designed to have a surface tension that penetrates and adheres to the nasal sinuses or cavity. The Saunders Manual does not teach or suggest the methods of treatment of chronic sinusitis nor methods of treatment of chronic sinusitis by administering as an aerosol a composition that has a surface tension that results in penetration or adhesion of the agent in the sinuses to effect such penetration, deposition or retention. Therefore, Saunders Manual does not cure the deficiencies in the teachings of Rubin *et al.* or Schmitt *et al.* nor any combination thereof.

Therefore the Examiner has failed to set forth a *prima facie* case of obviousness.

ANALYSIS

1. There would have been no motivation to have combined the teachings of Rubin *et al.* with those of Schmitt *et al.* and Saunders Manual to arrive at the instantly claimed methods

Rubin *et al.* and Schmitt *et al.* focus on treatment of lung conditions such as chronic lung diseases and pulmonary infections, particularly disorders in which the etiology involves a problem with pulmonary surfactant. Neither reference, singly or in any combination, teaches or suggests any treatments for any type of sinusitis, such as chronic sinusitis. Neither reference teaches or

suggests methods for delivery of agents to the nasal sinuses that could be used to treat chronic sinusitis.

Saunders Manual teaches only treatments for acute sinusitis and does not address treatments of chronic sinusitis or the need for treatments of chronic sinusitis; Saunders Manual does not address treatments of lung disease. Saunders Manual teaches general diagnosis and treatment of sinusitis. Saunders Manual does not teach or suggest any treatments for chronic lung diseases.

Thus, there is no motivation in any of the references that could be used by one of ordinary skill in the art to have combined the teachings of Rubin *et al.* and Schmitt *et al.* with those of the Saunders manual.

Notwithstanding this failure, the combination of teachings does not result in the instantly claimed methods.

2. The combination of teachings of the cited references does not result in the instantly claimed methods

Neither Rubin *et al.*, Schmitt *et al.*, nor Saunders Manual, singly or in any combination, teaches or suggests any methods for treatment of chronic sinusitis, nor compositions of betamethasone and a surfactant with a surface tension effective for deposition, penetration or retention of the composition in the nasal sinuses, nor any effecting deposition, penetration or retention of any composition the nasal cavity.

As noted above, the instant claims are directed to

a) methods of treatment of **chronic sinusitis**

b) by administering to a subject who has chronic sinusitis an aerosolized composition that has a surface tension effective for deposition, penetration or retention in the nasal sinuses

c) to effect such deposition, penetration or retention of a composition in the nasal sinuses to thereby treat chronic sinusitis.

As discussed above, none of the cited references singly nor any combination thereof teaches or suggests:

(1) any methods for the treatment of chronic sinusitis;

(2) nasally administering a composition as an aerosol to a subject with chronic sinusitis;

(3) effecting deposition, penetration or retention of a composition in the nasal sinuses to thereby treat chronic sinusitis.

Therefore, the combination of teachings of the cited references is deficient and the Examiner has failed to set forth a *prima facie* case of obviousness.

Rebuttal to the Examiner's comments in the Office Action

1. It appears that the Office Action has rejected the claims as though they are composition claims not method claims. All arguments in the Office Action are directed to the compositions, not to the method of treating chronic sinusitis. As noted above, none of the cited references even mentions chronic sinusitis.

The Office Action cites *In re Spada* for the premise that if the prior art teaches an identical chemical structure, the properties the applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Applicant respectfully submits that the claims addressed in *In re Spada* are composition claims, 911 F.2d at 708 n.4, whereas the claims of the instant application are methods claims. Although one can not claim compositions identical to those already patented, new and unobvious uses of old structures and compositions may be patentable (MPEP §2112.02).

The claims of the instant application are directed to **methods** of treating chronic sinusitis, a condition previously untreatable with methods known in the art. The methods are not taught or suggested by any of the cited references singly or in combination, since for example, none of the references, singly or in

any combination thereof, teaches or suggests treatments for chronic sinusitis. Further, none of the references, singly or in combination, teaches or suggests methods of treatment of chronic sinusitis by administering aerosolized compositions of betamethasone and a surfactant and effecting deposition, penetration or retention to the sinuses or nasal cavity to thereby treat chronic sinusitis.

2. The Office Action alleges that properties of the compositions used in the methods are inherent in the prior art and thus the claimed methods are obvious. As noted above, whether or not the compositions are obvious is irrelevant to a determination of the obviousness of methods of treatment of a particular disorder using a composition. A new method of use of a known composition is patentable and cannot be "inherent" in a composition. The compositions in the cited reference are for treatment of lung disorders. Use of such compositions, assuming *arguendo* that such compositions are those used in the instant methods, for treatment of chronic sinusitis is not inherent in a method of treatment of lung diseases involving inhibition of pulmonary surfactant.

Further, the use of inherency is not proper in an obviousness rejection. The Office Action alleges that the properties of the instantly claimed compositions are inherent in the compositions of Rubin *et al.*, and therefore the properties that the applicant discloses and/or claims are necessarily present. Applicant respectfully submits that the use of inherency is not proper in an obviousness rejection under 35 U.S.C. §103. "That which may be inherent in not necessarily known. Obviousness can not be predicated on what is unknown" (*In re Rijckaert*, 9 F.3d 1531, 1538, Fed. Cir. 1995, quoting *In re Spormann*). Obviousness can not be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. MPEP §2141.03 quoting *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

Furthermore, although inherency on rare occasion may be used as an argument in an anticipation rejection coupled with an obvious rejection for a composition (a 102/103 rejection, as described MPEP §2112), inherency is not proper in an obviousness rejection that stands alone under 35 U.S.C. §103. The Office Action does not set forth a 102/103 rejection. Additionally, Applicant respectfully submits that none of the references anticipates the instantly claimed methods and thus there is no basis for such a rejection.

3. The Office Action also alleges that Applicant in the response filed August 28, 2003 (hereinafter "previous response") addressed the cited references individually. Applicant respectfully submits that the combination of the references was addressed (see pages 15-18 of previous response). The arguments above, clearly address the combinations of teachings of the cited references. The teachings of each reference are discussed separately and then the analysis demonstrates (a) no motivation to combine; and (b) that such combination, even if there were motivation, does not result in the instantly claimed methods. Therefore, in this response as well as in the previous response, the rejection is rebutted by addressing the combination of teachings of the cited references.

4. The Office Action alleges that Rubin *et al.* teaches an anti-inflammatory that is inhaled for obstruction of the upper respiratory tract. It is respectfully submitted that this statement is incorrect. Rubin *et al.* teaches distribution of an anti-inflammatory to the lower respiratory tract by clearing the upper respiratory tract so that the agent is delivered to the lungs. Thus, the treatment of Rubin *et al.* is not for the treatment of sinusitis or the nasal passages, but for treatment of the lungs to clear the airway obstruction in the upper respiratory tract and treat the lower respiratory tract.

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In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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